New Retinal PHYSICIAN

A Practice Primer for the Beginning Retina Specialist

AMD: WHAT ARE WE MISSING?

Developing an educational program to reduce missed diagnoses

Vivienne S. Hau, MD, PhD

– PAGE 8

A Publication of Retinal PHYSICIAN

PentaVision

Why We Added the NGENUITY® System to Our Surgery Center

By enhancing the surgeon's view, Alcon's 3D Visualization System positively impacts patient care

Wolfe Eye Clinic has been serving patients in Iowa for 99 years, maintaining through the decades its commitment to providing high-quality, technology-driven care. "We've always been involved in innovation — implementing and advancing the newest technology to improve the care of our patients," says **Jared S. Nielsen, MD, MS, MBA**, a vitreoretinal surgeon with Wolfe Surgery Center and Wolfe Eye Clinic, which has multiple locations throughout Iowa. "When I saw the performance of the NGENUITY® 3D Visualization System during my demo in our OR, it became clear to me that this is good for patients, and we elected to purchase it for our surgery center."

MUCH MORE THAN COOL

When other surgeons learn Dr. Nielsen is using the NGENUITY® 3D Visualization System, they want to hear about it. "I get the sense that some see the technology as interesting and fun, maybe a cool marketing tool, but without first-hand experience, they aren't sure how it can enhance their practice," he says. "I tell them NGENUITY® has been helpful in marketing to referring doctors, but for me, the main benefit is better patient care. The system improves my abilities in the OR. I use a very good, state-of-the-art surgical microscope, but adding the NGENUITY® with its digital visualization, enhanced stereopsis, and high magnification is amazing. Surgery is all about visualization. The better you can see what you're doing, the better you're able to precisely address pathology and perform at a higher level."

Compared to traditional analog microscopes, NGENUITY® delivers up to 48% greater magnification, up to 5 times extended depth of field, and up to 42% finer depth resolution.[1] In addition, Dr. Nielsen notes, "There's a potential safety advantage with the NGENUITY® 3D Visualization System because electronic amplification of the camera's signal creates a brighter image on the display,[2] allowing me to operate using less light than I had in the past. I use 27-gauge instrumentation, and I've cut my light pipe intensity by 60% and my chandelier intensity by 30%."

Dr. Nielsen is as pleased with the ergonomics of the NGENUITY® 3D Visualization System as he is with the view it provides. Rather than looking through the microscope eye-piece, the surgeon sees the surgical field in 3D on the nearby high-definition screen. "Using a traditional microscope — even with great technology, a great chair, and a great adjustable bed — the fact of the matter is you have to hold your eyes in a very specific spot. With a whole day of cases, that's quite strenuous. He continues, "I worked with an ergonomics specialist early in my career to learn to sit properly to avoid strain, but I can still feel it in my back and neck at the end of a busy day. After we got our NGENUITY® system setup optimized, I really began to appreciate how much I enjoy not having to retain that fixed posture because of the microscope demands." Working with others in the OR, such as fellows, is easier, too. Dr. Nielsen says, "It's amazing how well we can all see."

NEW SOFTWARE INTEGRATES AND STREAMLINES

The DATAFUSION (1.2) software integrates the CONSTELLATION® Vision System and the NGENUITY® 3D Visualization System, allowing surgeons to track key surgical parameters — such as intraocular pressure, flow rates, infusion pressure, and laser power — in real-time on one screen. Data from the CONSTELLATION® can be displayed on the 16:9 aspect ratio NGENUITY® screen in

the four corners that aren't occupied by the circular image of the eye.

Other upgrades for improved functionality, procedure flow, and surgeon control include the addition of four preset imaging modes, two footswitch control options, advanced 2D or 3D video capture, and enhancement of the user interface to enable a streamlined white balancing process.

VERSATILITY = VALUE

Dr. Nielsen began using the NGENUITY® 3D Visualization System for macular cases only, but now uses it exclusively in all of his macular and vitreoretinal surgeries. "I also do anterior segment cases from time to time and have used the NGENUITY® 3D Visualization System to perform cataract surgery and IOL exchanges," he says. "I'm comfortable using the system in every situation in the operating room."

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Dr. Nielsen has received compensation from Alcon for this article.

CONSTELLATION® SYSTEM WITH PUREPOINT® LASER BRIEF STATEMENT
CAUTION: Federal law restricts this device to sale by, or on the order of, a physician.

INDICATIONS FOR USE: The CONSTELLATION® Vision System is an ophthalmic microsurgical system that is indicated for both anterior segment (i.e., phacoemulsification and removal of cataracts) and posterior segment (i.e., vitreoretinal) ophthalmic surgery.

The ULTRAVIT® Vitrectomy Probe is indicated for vitreous cutting and aspiration, membrane cutting and aspiration, dissection of tissue and lens removal. The valved entry system is indicated for scleral incision, canulae for posterior instrument access and venting of valved cannulae. The infusion cannula is indicated for posterior segment infusion of liquid or gas.

The PUREPOINT® Laser is indicated for use in photocoagulation of both anterior and posterior segments of the eye including:

- Retinal photocoagulation, panretinal photocoagulation and intravitreal endophotocoagulation of vascular and structural abnormalities of the retina and choroid including: Proliferative and nonproliferative retinopathy (including diabetic); choroidal neovascularization secondary to age-related macular degeneration; retinal tears and detachments; macular edema, retinopathy of prematurity; choroidal neovascularization; leaking microaneurysms.
- Iridotomy/Iridectomy for treatment of chronic/primary open angle glaucoma, acute angle closure glaucoma and refractory glaucoma.
- Trabeculoplasty for treatment of chronic/primary open angle glaucoma and refractory glaucoma.
- And other laser treatments including: internal sclerostomy; lattice degeneration; central and branch retinal vein occlusion; suturelysis; vascular and pigment skin lesions.

The FlexTip* laser probe is intended to be used with ALCON® 532nm laser systems.

CONTRAINDICATIONS:
- Patients with a condition that prevents visualization of target tissue (cloudy cornea, or extreme haze of the aqueous humor of the anterior chamber of vitreous humor) are poor candidates for LIO delivered laser treatments.
- The infusion cannula is contraindicated for use of oil infusion.

COMPLICATIONS: Corneal burns, inflammation, loss of best-corrected visual acuity, loss of visual field and transient elevations in intraocular pressure can occur as a result of ophthalmic laser treatment. Unintentional retinal burns can occur if excessive treatment beam power or duration is used.

WARNINGS AND PRECAUTIONS:
- The disposables used in conjunction with ALCON® instrument products constitute a complete surgical system. Use of disposables and handpieces other than those manufactured by Alcon may affect system performance and create potential hazards.
- Attach only Alcon supplied consumables to console and cassette luer fittings. Do not connect consumables to the patient's intravenous connections.
- Mismatch of consumable components and use of settings not specifically adjusted for a particular combination of consumable components may create a patient hazard.
- Vitreous traction has been known to create retinal tears and retinal detachments.
- The closed loop system of the CONSTELLATION® Vision System that adjusts IOP cannot replace the standard
- of care in judging IOP intraoperatively. If the surgeon believes that the IOP is not responding to the system settings and is dangerously high or low, this may represent a system failure. **NOTE:** To ensure proper IOP Compensation calibration, place infusion tubing and infusion cannula on a sterile draped tray at mid-cassette level during the priming cycle.
- Leaking sclerotomy may lead to post operative hypotony.
- Back scattered radiation is of low intensity and is not harmful when viewed through a protective filter. All personnel in the treatment room must wear protective eyewear, OD4 or above at 532nm, when the system is in Standby/Ready mode as well as during treatment. The doctor protection filter is an OD greater than 4 at 532nm.

ATTENTION: Please refer to the CONSTELLATION® Vision System Operators Manual for a complete listing of indications, warnings, and precautions.

*Trademarks are property of their respective owners.

IMPORTANT PRODUCT INFORMATION FOR NGENUITY® 3D VISUALIZATION SYSTEM FOR THE DIGITALLY ASSISTED VITREORETINAL SURGERY PLATFORM

IMPORTANT PRODUCT INFORMATION

CAUTION: Federal (USA) law restricts this device to sale by, or on the order of, a physician.

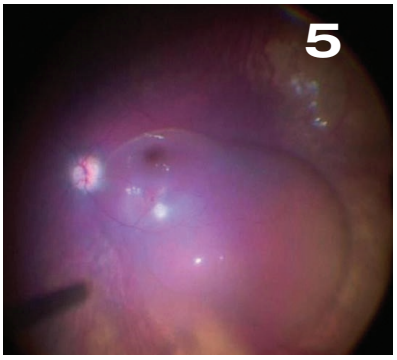
INDICATION: The NGENUITY® 3D Visualization System consists of a 3D stereoscopic, high-definition digital video camera and workstation to provide magnified stereoscopic images of objects during micro-surgery. It acts as an adjunct to the surgical microscope during surgery displaying real-time images or images from recordings.

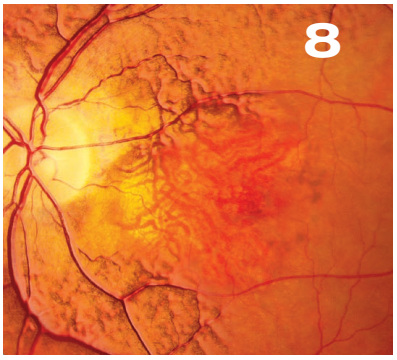
WARNINGS: The system is not suitable for use in the presence of flammable anesthetics mixture with air or oxygen. There are no known contraindications for use of this device.

PRECAUTIONS: Do not touch any system component and the patient at the same time during a procedure to prevent electric shock. When operating in 3D, to ensure optimal image quality, use only approved passive-polarized glasses. Use of polarized prescription glasses will cause the 3D effect to be distorted. In case of emergency, keep the microscope oculars and mounting accessories in the cart top drawer. If there are any concerns regarding the continued safe use of the NGENUITY® 3D Visualization System, consider returning to using the microscope oculars.

ATTENTION: Refer to the User Manual for a complete list of appropriate uses, warnings and precautions.

Table of Contents





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Making History

Exploring Luxturna gene therapy and its surgical delivery

BY CHRISTINA Y. WENG, MD, MBA

In 2017, medical history was made when voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics) received FDA approval and became the first gene therapy targeting a disease caused by specific gene mutations to be approved in the United States. The implications of this are truly profound, as a once-untreatable class of diseases suddenly became treatable. Reaching this point reflects a culmination of research efforts spanning decades and unlocks an array of promising possibilities in the field of inherited retinal diseases.

OVERVIEW

Voretigene neparvovec-rzyl is an adeno-associated virus vector (AAV)-based subretinal gene therapy indicated for patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy and viable retinal cells as determined by the treating physician(s). Biallelic mutations of the *RPE65* gene disrupt the visual cycle and lead to accumulation of toxic byproducts in the retinal pigment epithelial (RPE) cells. *RPE65* mutations cause 8-16% of Leber congenital amaurosis diagnoses and 1-3% of retinitis pigmentosa diagnoses.[1-4] Symptoms and age of onset are variable, but affected patients generally complain of nyctalopia, peripheral field loss, and blurry vision, all of which usually progress over time. Subretinal injection of Luxturna induces transduction of some RPE cells with a cDNA encoding normal RPE65 protein.

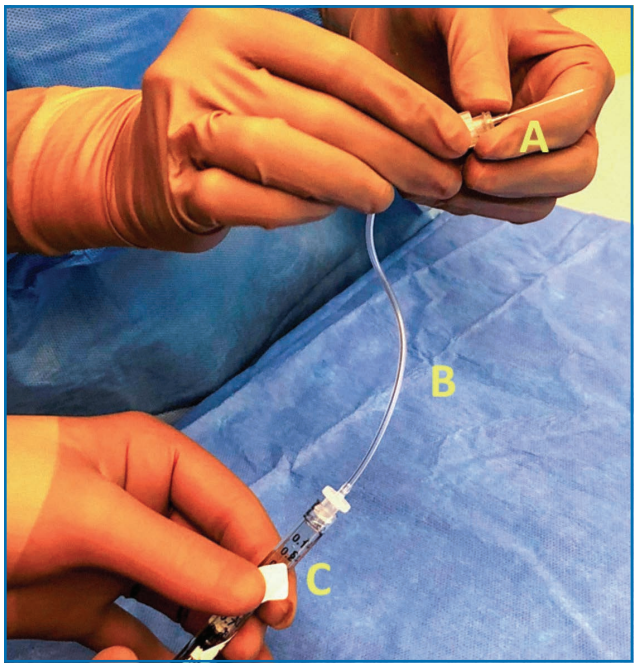
CLINICAL STUDIES

Phase 1 studies of voretigene neparvovec-rzyl commenced in 2007, 10 years after *RPE65* mutations were first identified. Given the favorable safety profile in 12 subjects, the highest tested drug dose (1.5×10^{11} vector genomes [vg] in 0.3 mL) was selected for use in future trials. The Phase 3 study (NCT00999609) completed enrollment of its 31 subjects ≥4 years of age in 2013. Control group subjects had the option to cross over to receive treatment after the first year post-enrollment, and all elected to proceed in this trial. Following pars plana vitrectomy, the drug was delivered as a 0.3 mL subretinal injection along the superior vascular arcade using a microtip cannula. Air-fluid exchange was performed with the intention to remove circulating vectors and tamponade the injection site. The second eye was injected 6 to 18 days later. The primary endpoint was functional vision measured by the Multi-Luminance Mobility Test (MLMT), which uses a mobility course to test subjects at light levels ranging from 1-400 lux. Other measured outcomes included full-field light sensitivity threshold (FST), which measures lowest illumination detected over the entire retina, visual acuity (VA), and visual field.

At year 1, the mean bilateral MLMT change score was 1.8 (SD 1.1) light levels in the treatment arm versus 0.2 (SD 1.0) in the control group (difference of 1.6, 95% CI 0.72-2.41, p=0.0013), and there was a 100-fold FST improvement in treated patients. Thirteen (65%) of 20 treated subjects, but no control participants, passed the MLMT at the lowest luminance level. VA improvements in those treated were modest, but not statistically significant. No serious adverse events related to the product or its administration, such as a clinically significant cytotoxic T-cell response to AAV2 or RPE65, were observed at 1 year.[5] These positive effects have been sustained for at least 3 years, as recently presented by Stephen Russell, MD, professor of ophthalmology at University of Iowa, at the 2018 Annual Meeting of the American Society of Retina Specialists.[6]

POST-FDA APPROVAL

Following FDA approval, Spark Therapeutics proceeded with a staged product rollout. There are currently nine treatment centers administering Luxturna: Baylor College of Medicine, University of Iowa, Massachusetts Eye & Ear Infirmary, Bascom Palmer Eye Institute, Children's Hospital of Philadelphia, Cincinnati Children's Hospital, Casey Eye Institute, Children's Hospital Los Angeles, and Scheie Eye Institute. All participating surgeons have completed the Spark Therapeutics Surgical Education Program. Given its first-in-class status as an ophthalmic gene therapy, several important precedents have been set in terms of pricing (the drug is priced at $425,000 per eye), distribution



Courtesy of Christina Y. Weng, MD, MBA

Figure 1. Setup of the injection apparatus includes a 41-gauge subretinal injection cannula (A) connected by a polyvinyl chloride extension tube (B) to the disposable syringe containing 0.8 mL of voretigene neparvovec-rzyl (C).

(Express Scripts has partnered with Spark Therapeutics for distribution and specialty pharmacy services, circumventing a buy-and-bill model), and payer agreements (outcomes-based pricing is being practiced in certain plans).

PRE-OPERATIVE PLANNING

Careful planning is critical to ensure treatment success. When a potential candidate is identified, genetic testing must be performed to confirm that a biallelic *RPE65* mutation is present; ancillary tests, which may include visual fields, perimetry, electroretinogram, optical coherence tomography, autofluorescence, FST, and fundus photography, may guide assessment of a patient's visual potential. If the decision is made to move forward, detailed patient counseling is imperative to discuss expectations, risks, and benefits of treatment. Additionally, the benefits investigation should be initiated at this point. Spark Therapeutics offers a program called Generation Patient Services to assist in this process as well as to navigate reimbursement, coverage, travel logistics, and out-of-pocket costs.

Once a surgery date has been set, it is important to disseminate logistical information to all involved parties. Aaron Nagiel, MD, PhD, assistant professor of ophthalmology at University of Southern California/Children's Hospital Los Angeles, best describes the process: "[It's] truly a team effort. A diligent clinical coordinator, adept pharmacists, and experienced OR staff are just a few examples of essential personnel that facilitate a smooth surgical delivery."

Our facility found it extremely beneficial to rehearse day-of-surgery events 1 to 2 weeks prior to the actual operation, especially because our institutional pharmacy is geographically distanced from the surgical center, which adds one additional drug transfer point. A practice run-through also allows the pharmacy staff to review the drug preparation process and provides the surgical team an opportunity to handle the supplies.

SURGICAL DELIVERY OF LUXTURNA

With regard to Luxturna delivery, there are numerous variations in surgical approach and technique. Therefore, although a few approaches are discussed in this section, this does not imply that one is more effective than others.

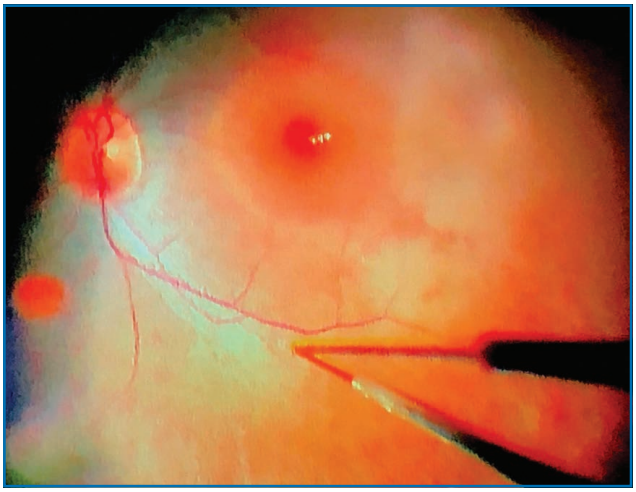
Luxturna should be administered in an aseptic environment. Two prepared syringes (one for back-up) with 0.8 mL of diluted drug each should be provided by pharmacy personnel. A 41-gauge subretinal injection cannula with a polyamide microtip and a polyvinyl chloride extension tube with an inner diameter of ≤1.4 mm and length of ≤15.2 cm are also needed in addition to the normal set-up for a pars plana vitrectomy.[7]

Many surgeons prefer general anesthesia for their patients either because of pediatric age or to minimize movement. The eye should be prepared and draped as per normal sterile protocol. Connect the first syringe to the extension tube and subretinal injection cannula (Figure 1). Prime the apparatus by injecting until droplets are seen at the cannula tip; some elect to then continue injecting until the plunger tip aligns with the 0.3 mL mark so that the intended delivery volume is set; others prefer to bypass this step in the event that additional drug is needed.

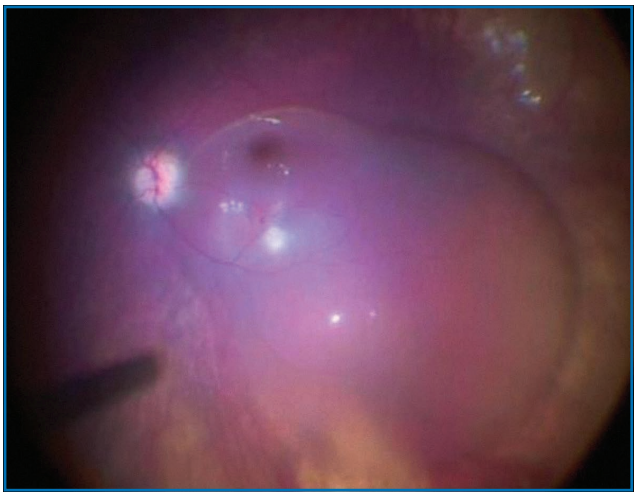
A standard 3-port pars plana vitrectomy should be performed using any gauge of choice. Most agree that the posterior hyaloid should be elevated; avoid triamcinolone acetonide stain, if possible.

"Interestingly, the vitreoretinal interface in these patients tends to make the hyaloid quite easy to detach, even in younger children," says Audina Berrocal, MD, professor of ophthalmology at Bascom Palmer Eye Institute.

Once complete, the intended site of administration should be identified. Ideally, this is located along the superotemporal arcade, at least 2 mm distal to the foveal center, and not in direct contact with retinal vessels or areas with pathologic features. Some surgeons will cut a bevel at the cannula tip to facilitate entry into the subretinal space. Regarding its insertion through the port, "We found it helpful to remove



Courtesy of Tahira Scholle, MD, and J. Timothy Stout, MD, MBA, PhD, Baylor College of Medicine



Courtesy of Aaron Nagiel, MD, PhD, University of Southern California

Figure 2. (Left) Surgeon's view of patient's right eye illustrating the recommended site of subretinal injection along the superotemporal arcade at least 2 mm away from the foveal center, avoiding major vessels or areas of pathologic changes. Figure 3. (Right) Subretinal bleb in patient's right eye following injection of 0.3 mL of voretigene neparvovec-rzyl (1.5 x 10^{11} vg).

the valve of the superotemporal cannula with 0.12 forceps to prevent kinking of the subretinal cannula," advises Tahira Scholle, MD, assistant professor of ophthalmology at Baylor College of Medicine.

While the surgical assistant is holding the syringe, the surgeon will bury the cannula tip into the intended injection site (Figure 2) and tell the assistant to begin slowly injecting until a subretinal bleb is visualized. Recently, some surgeons have utilized a foot pedal-assisted method to inject the vector. A total volume of 0.3 mL (1.5 x 10^{11} vg) should be delivered (Figure 3). In cases where it is difficult to raise a subretinal bleb, some have used balanced salt solution or even air to initiate a bleb and then subsequently injected the drug into it; how this affects drug concentration or localization is not fully understood at this time.

After completing the injection, retract the subretinal cannula from the eye and discard all unused product per local biosafety guidelines. Perform an air-fluid exchange, avoiding drainage near the retinotomy site. Proceed with closure as per normal protocol. Supine head positioning should be initiated immediately in the post-operative period and maintained as much as possible over the first 24 hours. Typical post-operative surveillance and drop regimen are followed in addition to a short course of oral corticosteroids (typically started 3 days prior to Luxturna administration). The second eye should be treated no sooner than 6 days after the first eye.

CONCLUSION

It is an exciting time for all retina specialists, especially for those in the early stages of their careers. Luxturna is not only the first FDA-approved targeted gene therapy, but also represents a giant leap forward for all patients with inherited retinal diseases. As our knowledge of genetic disorders and innovative gene therapies continues to advance, it is fathomable that we will be able to treat other gene mutation-associated conditions in the future. *NRP*

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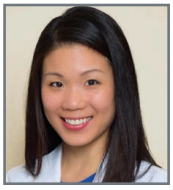

Dr. Weng is an assistant professor in the department of ophthalmology, division of vitreoretinal diseases and surgery, at the Baylor College of Medicine in Houston.

What Are We Missing?

Steps for developing an educational program to help reduce missed amd diagnoses

BY VIVIENNE S. HAU, MD, PHD

Are we missing signs of early AMD? According to recent research, the answer is yes. A cross-sectional study[1] of primary eyecare practices in Birmingham, AL, focused on 644 subjects who were 60 years or older with normal macular health based on their most recent dilated comprehensive eye examination by an ophthalmologist or optometrist. Researchers found that signs of AMD were missed on a quarter of otherwise seemingly normal eye exams.

Indeed, approximately 25% of eyes identified as normal by primary eyecare physicians based on dilated eye examination were found to have macular characteristics indicating AMD by fundus photography and trained raters. Thirty percent of undiagnosed eyes ultimately had AMD with large drusen that would have been treatable with nutritional supplements had it been diagnosed, according to the study.[1]

The study also discussed some of the characteristics of patients with missed diagnoses, which included older eyes, men, and those with less than a high school education. But it revealed no difference between phakia or pseudophakia or between optometrists versus ophthalmologists.

What's interesting is that cataract status or eyecare professional education had no bearing on missed diagnoses. In addition, one would assume a primary care eye doctor would scrutinize the maculas of their older patients more closely, as these patients are at higher risk for AMD. Perhaps the mostly white, non-Hispanic population in the study had more blonde fundi, or certain subjects were very photophobic, limiting a good evaluation. Nevertheless, a 1-in-4 rate of missed diagnoses is very high.

It's worth noting that this cohort stemmed from patients examined between 2009 and 2011. Since then, the practicality and cost of regular imaging use, such as fundus photography and OCT, has improved. It is possible that if this same cohort were examined today with more consistent use of such technology, there would be fewer missed diagnoses. OCT has been shown to be important in the diagnosis and management of AMD and is recommended by the American Academy of Ophthalmology Preferred Practice Patterns for AMD.[2,3]

In addition, new clinical and technological strategies to improve early detection of macular degeneration have been developed, and, if employed, could reduce the number of missed diagnoses (See "Early AMD Detection," page 10).

Yet, another important strategy to reduce missed AMD diagnoses, highlighted by the findings of the study,[1] is to focus on educating those at the center of the study: primary eyecare professionals and their patients. Indeed, the very real possibility that patients may not understand the importance of undergoing regular dilated eye exams, especially after age 50, and more often for those with a family history of AMD, limits the ability of primary eyecare professionals to diagnose AMD. In surveys in the U.S., Australia and Canada, only 20-30% of respondents indicated they were "very familiar" or "somewhat familiar" with AMD.[3,4] For a condition that is the leading cause of visual impairment in those over age 50 in the U.S,[5] it is a severe shortcoming in our health education that most patients do not know this.

Thus, retina specialists, in particular, are presented with an opportunity to be at vanguard of educational efforts to help reduce missed AMD diagnoses and thereby help to prevent vision loss. Early AMD diagnosis means earlier intervention, and it's been shown that earlier intervention leads to better outcomes in AMD treatment.[6]

COMPONENTS OF AN AMD EDUCATIONAL CAMPAIGN

Like any good messaging effort, a comprehensive AMD educational campaign addresses the key questions of who or what, where, when, how, and why, with the level of detail and clinical or scientific terminology and concepts varying depending on your audience (ophthalmologists, optometrists, general public, or the community from which you are likely to draw your patients).

In addition, the campaign must target the motivations and interests of each group, which will differ as well. Gearing your campaign's efforts toward the interests of each group will make your message more interesting. This doesn't mean the motivations are mutually exclusive, but emphasizing certain components over others will be helpful. Indeed, there will be many opportunities to educate at all levels.

LEVERAGE MULTIPLE PLATFORMS

Depending on how far you take it, your AMD educational campaign can — and likely should — consist of multiple parts unfolding on multiple platforms, including speaking engagements for local community groups or events, brochures, interviews for TV news broadcasts and newspaper articles, a web page on your practice website, and a social media presence.

For your patients, in particular, having a good website with plenty of educational materials on AMD and ease of making appointments will be important, as will a social media presence with Facebook, Twitter, and Instagram. While your typical AMD patient may not be very tech savvy (although you'll be surprised how many of them are these days), younger family members who will be driving them to their appointments are likely to be active on social media. But remember: regular updates are extremely important. Even linking to a new article on AMD will be helpful if your time is too limited to regularly write new content. A website or social media account that hasn't been updated in a year or two looks worse than not having one at all.

As a retina specialist, you should make a point to leverage all available channels to expand your reach. In addition to in-house and online marketing, speak at local health fairs and community centers — especially those focused on seniors and adult communities. It's also a good idea to consider partnering with local ophthalmologists or going it alone with your own practice to present AMD awareness conferences for optometry CE credit. In addition, many hospital systems, not just universities, regularly hold grand rounds. Offering to speak at these events can get your name out to primary care physicians, while your lecture should demonstrate the necessity of stressing to patients the importance of having regular eye exams. Becoming active in your state and county medical societies can be a great way to network and present opportunities to deliver an AMD awareness lecture.

CONTENT IS KING

As discussed in the previous section, it is important to understand your target audience. Your AMD education campaign's "what" — or specific content — will vary by audience. For example, in targeting the community, you should stress the importance of regular eye exams, educate attendees on the symptoms of AMD (such as metamorphopsia, scotoma, photopsias, and decreased vision but discuss in layman's terms), and emphasize healthy lifestyle choices that can affect eye health. Healthy lifestyle choices include a diet rich in antioxidants with AREDS 2 vitamin supplementation, if indicated, exercise, and quitting smoking.

Content can be more complex when your audience consists of primary eyecare providers. An optometrist as part of a hospital system or a multispecialty practice versus one in solo private practice will have different incentives and business practices. Without wading into the details of scope of practice, I recommend that you keep in mind what your state allows and how that might affect your own recommendations on patient management. Speaking to an audience of ophthalmologists at a university versus multispecialty versus private practice will be different, as well.

In many ways, optometrists serve as the front line of eye care, as most patients will go to them first. This is why it is important to ensure they understand how to examine for and diagnose AMD. Remind them what clinical characteristics to look for, including how to determine intermediate drusen under difficult situations, such as a cloudy cornea/cataract with a blonde fundus. In addition, ensure that local optometrists always ask patients for an AMD family history and perform a comprehensive dilated eye exam on all patients older than 50.

As I mentioned earlier, imaging is increasingly being used for support and diagnosis. Fundus photography for baseline examination and OCT are key examples. In fact, a recent publication on automated drusen detection with *en face* OCT demonstrates the increasing usefulness of imaging in early detection and management.[7] Many optometrists today have OCTs and wide-field imaging. Educating them on how to interpret their images, if applicable, could turn into a potential referral.

Speaking of which, it is critical to educate optometrists on when to refer to a retina specialist for further evaluation and treatment. Providing your audience with examples of imaging

Early AMD Detection: Better monitoring technologies and strategies can lead to better outcomes

A 2017 *JAMA* article by Allen Ho and colleagues reviewed the baseline characteristics of various cohorts of large-scale AMD treatment studies and found similarities that led to improved visual outcomes.[1] Specifically, younger patients with choroidal neovascular lesions that were smaller and associated with better initial visual acuity were more likely to have better visual acuity up to 2 years after the initiation of AMD treatment. These characteristics can be maximized with earlier detection.

As physicians, we're often hyper-focused on determining what medicine works best for our patients. But this study suggests that an even better strategy is to encourage earlier detection. Besides improving patient and physician education, another approach is to improve patient monitoring. Indeed, many exciting new monitoring tools and strategies[2] are emerging to help us help patients take control of their AMD treatment. Here, we discuss a few of them.

Kaiser Permanente Early AMD Screening Program

The Eye Monitoring Program at Kaiser Permanente in Southern California has won numerous accolades for its diabetic retinopathy screenings.[3] Kaiser Permanente is also working to implement a similar strategy to catch progression of AMD early by standardizing eye evaluations with a centralized OCT reading center and regular Amsler Grid testing. Because OCT provides high-resolution, noninvasive, cross-sectional imaging, it may detect AMD progression before patients become symptomatic.[4,5]

Patients are enrolled once they are determined to have early AMD without any other eye conditions requiring regular exams by a primary eyecare professional. Each patient receives an OCT scan twice a year at their local clinics, and the images are evaluated by the Kaiser Permanente reading center. In addition, patients are contacted monthly about their home Amsler grid use. Patients who report a change or have new findings on OCT are seen by an ophthalmologist right away. This increases patient engagement in their care, potentially detects progression of disease faster, and limits frequent, unnecessary doctor visits in the early stages of AMD. More than 1,700 patients have been enrolled in this program in the last 4 years. An analysis of the data is forthcoming.

Preferential Hyperacuity Perimetry

A particularly promising development involves Preferential Hyperacuity Perimetry (PHP), which operates on a principle similar to that of Amsler grids. Although widely used because of their low cost and ease of use, Amsler grids have low sensitivity and specificity for AMD.[6] Developed to allow early detection of neovascular AMD with much greater sensitivity and specificity than the Amsler grid,[7] PHP can be used by patients at home on a patented technology called ForeseeHome (Notal Vision). A series of dotted lines are presented to the retina, stimulating a colinear set of retinal receptive fields that, in turn, are processed in the visual cortex. As in AMD, the originally straight lines are perceived with a shift disturbance in the retinal morphology. Patients test themselves on the device that automatically sends the results to a data center, which then sends them to an eyecare professional. Clinical Phase III trial (HOME study) results were so promising that early study termination was recommended.[8,9]

Artificial Intelligence in AMD

One of the hottest areas in research is using artificial intelligence (AI) to help doctors analyze data for earlier detection of certain diseases, such as cancer,[10] Alzheimer's,[11] and pneumonia.[12] Considering the large amount of data introduced by OCT for AMD, computerized analysis through machine learning (i.e., artificial intelligence) may overcome some limitations of subjective analysis. Several companies and researchers[13-17] are developing software to accomplish this. For example, Cirrus OCT devices (Carl Zeiss Meditec) employ the FDA-approved "Advanced RPE Analysis Tool," and it has proven to be effective.[18,19]

Notal Vision, the company behind the ForeseeHome, is also looking at AI for OCT automated AMD detection,[20] with its Home-OCT device.[21] Currently in development, the Home-OCT utilizes the company's Notal OCT Analyzer to analyze images taken at home between visits and notify physicians of any changes in the patient's condition. Should expense and logistics not be prohibitive, this could prove to be the ultimate in home-monitoring for AMD.

that shows early subtle neovascular changes can be helpful.

When educating optometrists, your goal should be to ensure they have all the tools they need to diagnose these patients, but also to understand when to refer and provide them the support to do so.

MESSAGING TO OPHTHALMOLOGISTS

Educating ophthalmologists can be similar to that of optometrists, but you must first determine what the referring general ophthalmologist is comfortable treating. Many younger practitioners want to do their own anti-VEGF injections, as this is a regular part of their residency education. If so, it would be beneficial to find out how they would like help in supporting their patients. In addition, educating them on the signs and symptoms of complications of AMD treatment, such as hypersensitivity reactions to anti-VEGFs and endophthalmitis, will help ensure these patients are promptly referred. Informing them about treatments coming through the pipeline will help them see you as a supportive colleague and good referral option, if needed, for certain patients.

DON'T OVERLOOK OTHER LOCAL PROVIDERS

It's also worth reaching out to your local primary care, urgent care, and emergency care physicians. As we now know, the training we had examining the eye in medical school was limited. Holding a grand rounds lecture at the

Shape-discrimination Hyperacuity

Another option is shape-discrimination hyperacuity (SDH), in which patients self-evaluate changes in the contours of shapes, such as circles, on a smartphone app called MyVisionTrack (myvisiontrack.com). Studies have demonstrated very high sensitivity with no effect from contrast reduction and little change in normal aging, two important potentially confounding factors in AMD patients.[22,23] The test is cleared by the FDA and available with a prescription. Data from the app are sent to a remote monitoring database that can send reminders and alert the prescribing physician of any persistent changes, thereby getting the patient in sooner for earlier detection and treatment.[24] The fact that the test can be downloaded to personal smartphones and other devices rather than to a proprietary device could make this option accessible to more patients.

Early Detection, Better Care

The importance of earlier AMD detection, whether through better education or better monitoring, cannot be overstated. Emerging technology is being developed to help us fight AMD much earlier — and more effectively — than ever before.

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local medical school, medical society, or hospital can be a great way to let others know what to look for with a simple direct ophthalmoscopic exam in someone who fits the profile of a high-risk AMD patient. Creating awareness that AMD is the leading cause of visual impairment in those over 50 helps to catch the disease when examining a patient with visual complaints. At a minimum, it reminds them to think about referring out as well.

THE "WHEN" OF YOUR CAMPAIGN

The timing of your educational campaign will take planning. Some practices employ marketing consultants, but you can do it on your own. Either way, it's important to map out certain events and actions over a period of 1 or 2 years in advance to ensure you don't miss valuable opportunities to get the word out about AMD and how you can help. Knowing when certain health fairs, community events, grand rounds, CE events, and state and county society meetings and conferences occur can help you select a timeframe for your campaign and avoid missing deadlines for article or speaking submissions.

Two examples: February is "AMD Awareness Month," and September hosts the international "AMD Awareness Week." Many groups are receptive to having AMD talks during these times. Preparing a news release and/or using a public relations firm can help you get some traction with local television stations or publications to publicize your talk.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- **Endophthalmitis** may occur following any intraocular surgical procedure or injection. Use proper aseptic injection technique when administering LUXTURNA, and monitor for and advise patients to report any signs or symptoms of infection or inflammation to permit early treatment of any infection.
- **Permanent decline in visual acuity** may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.
- **Retinal abnormalities** may occur during or following the subretinal injection of LUXTURNA, including macular holes, foveal thinning, loss of foveal function, foveal dehiscence, and retinal hemorrhage. Monitor and manage these retinal abnormalities appropriately. Do not administer LUXTURNA in the immediate vicinity of the fovea. Retinal abnormalities may occur during or following vitrectomy, including retinal tears, epiretinal membrane, or retinal detachment. Monitor patients during and following the injection to permit early treatment of these retinal abnormalities. Advise patients to report any signs or symptoms of retinal tears and/or detachment without delay.
- **Increased intraocular pressure** may occur after subretinal injection of LUXTURNA. Monitor and manage intraocular pressure appropriately.
- **Expansion of intraocular air bubbles** Instruct patients to avoid air travel, travel to high elevations or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. It may take one week or more following injection for the air bubble to dissipate. A change in altitude while the air bubble is still present can result in irreversible vision loss. Verify the dissipation of the air bubble through ophthalmic examination.
- **Cataract** Subretinal injection of LUXTURNA, especially vitrectomy surgery, is associated with an increased incidence of cataract development and/or progression.

Adverse Reactions

- In clinical studies, ocular adverse reactions occurred in 66% of study participants (57% of injected eyes), and may have been related to LUXTURNA, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.

A New Vision

for your patients with an inherited retinal disease (IRD)

LUXTURNA (voretigene neparvovec-rzyl) is a one-time gene therapy that improves functional vision in individuals with an IRD who have confirmed biallelic *RPE65* gene mutations and viable retinal cells.[1]

With LUXTURNA, patients experienced a clinically meaningful improvement in the ability to navigate at lower light levels.[1]

IMPORTANT SAFETY INFORMATION (CONT'D)

- The most common adverse reactions (incidence ≥ 5% of study participants) were conjunctival hyperemia (22%), cataract (20%), increased intraocular pressure (15%), retinal tear (10%), dellen (thinning of the corneal stroma) (7%), macular hole (7%), subretinal deposits (7%), eye inflammation (5%), eye irritation (5%), eye pain (5%), and maculopathy (wrinkling on the surface of the macula) (5%).

Immunogenicity
Immune reactions and extra-ocular exposure to LUXTURNA in clinical studies were mild. No clinically significant cytotoxic T-cell response to either AAV2 or RPE65 has been observed. In clinical studies, the interval between the subretinal injections into the two eyes ranged from 7 to 14 days and 1.7 to 4.6 years. Study participants received systemic corticosteroids before and after subretinal injection of LUXTURNA to each eye, which may have decreased the potential immune reaction to either AAV2 or RPE65.

Pediatric Use
Treatment with LUXTURNA is not recommended for patients younger than 12 months of age, because the retinal cells are still undergoing cell proliferation, and LUXTURNA would potentially be diluted or lost during the cell proliferation. The safety and efficacy of LUXTURNA have been established in pediatric patients. There were no significant differences in safety between the different age subgroups.

Please see a brief summary of the US Full Prescribing Information on the following pages.

Reference: 1. LUXTURNA [package insert]. Philadelphia, PA: Spark Therapeutics, Inc; 2017.

P-RPE65-US-360005 April 2018

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Brief Summary of US Full Prescribing Information for LUXTURNA (voretigene neparvovec-rzyl)

1 INDICATIONS AND USAGE
LUXTURNA (voretigene neparvovec-rzyl) is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physicians.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis
Endophthalmitis may occur following any intraocular surgical procedure or injection. Proper aseptic injection technique should be used when administering LUXTURNA. Following the injection, patients should be monitored to permit early treatment of any infection. Advise patients to report any signs or symptoms of infection or inflammation without delay.

5.2 Permanent decline in visual acuity
Permanent decline in visual acuity may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.

5.3 Retinal abnormalities
Retinal abnormalities may occur during or following the subretinal injection of LUXTURNA, including macular holes, foveal thinning, loss of foveal function, foveal dehiscence, and retinal hemorrhage. Monitor and manage these retinal abnormalities appropriately. LUXTURNA must not be administered in the immediate vicinity of the fovea. *[See Dosage and Administration (2.3) in full prescribing information]*

Retinal abnormalities may occur during or following vitrectomy, including retinal tears, epiretinal membrane, or retinal detachment. Monitor patients during and following the injection to permit early treatment of these retinal abnormalities. Advise patients to report any signs or symptoms of retinal tears and/or detachment without delay.

5.4 Increased intraocular pressure
Increased intraocular pressure may occur after subretinal injection of LUXTURNA. Monitor and manage intraocular pressure appropriately.

5.5 Expansion of intraocular air bubbles
Instruct patients to avoid air travel, travel to high elevations, or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. It may take one week or more following injection for the air bubble to dissipate. A change in altitude while the air bubble is still present can result in irreversible vision loss. Verify the dissipation of the air bubble through ophthalmic examination.

5.6 Cataract
Subretinal injection of LUXTURNA, especially vitrectomy surgery, is associated with an increased incidence of cataract development and/or progression.

6 ADVERSE REACTIONS
The most common adverse reactions (incidence ≥5%) were conjunctival hyperemia, cataract, increased intraocular pressure, retinal tear, dellen (thinning of the corneal stroma), macular hole, subretinal deposits, eye inflammation, eye irritation, eye pain, and maculopathy (wrinkling on the surface of the macula).

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of other products and may not reflect the rates observed in practice.

The safety data described in this section reflect exposure to LUXTURNA in two clinical trials consisting of 41 subjects (81 eyes) with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Forty of the 41 subjects received sequential subretinal injections of LUXTURNA to each eye. One subject received LUXTURNA in only one eye. Seventy-two of the 81 eyes were exposed to the recommended dose of LUXTURNA at 1.5×10^{11} vg; 9 eyes were exposed to lower doses of LUXTURNA. Study 1 (n=12) was an open-label, dose-exploration safety study. Study 2 (n=29) was an open-label, randomized, controlled study for both efficacy and safety *[see Clinical Studies (14) in full prescribing information]*. The average age of the 41 subjects was 17 years, ranging from 4 to 44 years. Of the 41 subjects, 25 (61%) were pediatric subjects under 18 years of age, and 23 (56%) were females.

Twenty-seven (27/41, 66%) subjects had ocular adverse reactions that involved 46 injected eyes (46/81, 57%). Adverse reactions among all subjects in Studies 1 and 2 are described in Table 1. Adverse reactions may have been related to LUXTURNA, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.

Table 1. Ocular Adverse Reactions Following Treatment with LUXTURNA (N=41)

Adverse Reactions	Subjects n=41	Treated Eyes n=81
Any ocular adverse reaction	27 (66%)	46 (57%)
Conjunctival hyperemia	9 (22%)	9 (11%)
Cataract	8 (20%)	15 (19%)
Increased intraocular pressure	6 (15%)	8 (10%)
Retinal tear	4 (10%)	4 (5%)
Dellen (thinning of the corneal stroma)	3 (7%)	3 (4%)
Macular hole	3 (7%)	3 (4%)
Subretinal deposits*	3 (7%)	3 (4%)
Eye inflammation	2 (5%)	4 (5%)
Eye irritation	2 (5%)	2 (2%)
Eye pain	2 (5%)	2 (2%)
Maculopathy (wrinkling on the surface of the macula)	2 (5%)	3 (4%)
Foveal thinning and loss of foveal function	1 (2%)	2 (2%)
Endophthalmitis	1 (2%)	1 (1%)
Foveal dehiscence (separation of the retinal layers in the center of the macula)	1 (2%)	1 (1%)
Retinal hemorrhage	1 (2%)	1 (1%)

*Transient appearance of asymptomatic subretinal precipitates inferior to the retinal injection site 1-6 days after injection.

Immunogenicity
At all doses of LUXTURNA evaluated in Studies 1 and 2, immune reactions and extra-ocular exposure were mild. In Study 1 (n=12), the interval between the subretinal injections into the two eyes ranged from 1.7 to 4.6 years. In Study 2, the interval between the subretinal injections into the two eyes ranged from 7 to 14 days. No subject had a clinically significant cytotoxic T-cell response to either AAV2 or RPE65.

Subjects received systemic corticosteroids before and after subretinal injection of LUXTURNA to each eye. The corticosteroids may have decreased the potential immune reaction to either vector capsid (adeno-associated virus serotype 2 [AAV2] vector) or transgene product (retinal pigment epithelial 65 kDa protein [RPE65]).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary: Adequate and well-controlled studies with LUXTURNA have not been conducted in pregnant women. Animal reproductive studies have not been conducted with LUXTURNA. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation
Risk Summary: There is no information regarding the presence of LUXTURNA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUXTURNA and any potential adverse effects on the breastfed infant from LUXTURNA.

8.3 Females and Males of Reproductive Potential
No nonclinical or clinical studies were performed to evaluate the effect of LUXTURNA on fertility.

8.4 Pediatric Use
Treatment with LUXTURNA is not recommended for patients younger than 12 months of age because the retinal cells are still undergoing cell proliferation, and LUXTURNA would potentially be diluted or lost during cell proliferation.

The safety and efficacy of LUXTURNA have been established in pediatric patients. Use of LUXTURNA is supported by Study 1 and Study 2 *[see Clinical Studies (14) in full prescribing information]* that included 25 pediatric patients with biallelic *RPE65* mutation-associated retinal dystrophy in the following age groups: 21 children (age 4 years to less than 12 years) and 4 adolescents (age 12 years to less than 17 years). There were no significant differences in safety between the different age subgroups.

8.5 Geriatric Use
The safety and effectiveness of LUXTURNA have not been established in geriatric patients. Clinical studies of LUXTURNA for this indication did not include patients age 65 years and over.

17 PATIENT COUNSELING INFORMATION
Advise patients and/or their caregivers of the following risks:

Endophthalmitis and other eye infections: Serious infection can occur inside of the eye and may lead to blindness. In such cases, there is an urgent need for management without delay. Advise patients to call their healthcare provider if they experience new floaters, eye pain, or any change in vision.

Permanent decline in visual acuity: Permanent decline in visual acuity may occur following subretinal injection of LUXTURNA. Advise patients to contact their healthcare provider if they experience any change in vision.

Retinal abnormalities: Treatment with LUXTURNA may cause some defects in the retina such as a small tear or a hole in the area or vicinity of the injection. Treatment may cause thinning of the central retina or bleeding in the retina. Advise patients to follow up with their healthcare provider on a regular basis and report any symptoms, such as decreased vision, blurred vision, flashes of light, or floaters in their vision without delay.

Increased intraocular pressure: Treatment with LUXTURNA may cause transient or persistent increase in intraocular pressure. If untreated, such increases in intraocular pressure may cause blindness. Advise patients to follow up with their healthcare provider to detect and treat any increase in intraocular pressure.

Expansion of intraocular air bubbles: Advise patients to avoid air travel, travel to high elevations, or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. A change in altitude while the air bubble is still present may cause irreversible damage.

Cataract: Advise patients that following treatment with LUXTURNA, they may develop a new cataract, or any existing cataract may get worse.

Shedding of LUXTURNA: Transient and low-level shedding of LUXTURNA may occur in patient tears. Advise patients and/or their caregivers on proper handling of waste material generated from dressing, tears, and nasal secretion, which may include storage of waste material in sealed bags prior to disposal. These handling precautions should be followed for up to 7 days following LUXTURNA administration.

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It can increase your name recognition and may even lead to additional opportunities on TV or with national publications. Once you've done a good job with a few of these talks, you'll soon develop a reputation and potentially become a "go to" person for future questions/stories about eye-related issues.

THE "HOW" OF YOUR CAMPAIGN

As a new retinal specialist, who is likely dealing with many other issues of growing your practice, how do you find the time and resources to plan, launch, and carry out such an ambitious campaign aimed at reducing missed AMD diagnoses? It can be challenging. But chances are you know a fellow retina colleague who can help. Networking is invaluable; attending the various retina meetings throughout the year can build upon the contacts you made through training. I recommend the American Society of Retina Specialists (ASRS) Business of Retina meeting that occurs every Spring, as this is a meeting focused purely on the practice management side of retina. It attracts nearly 500 managing retina practice physicians and administrators. You can also partner with local referring doctors or medical societies to share the burden of developing resources for a campaign. This has the side benefit of strengthening your relationship with these fellow colleagues.

Practice consultants and marketing specialists who work specifically with ophthalmology practices can also provide you with direction and expertise. Again, conferences like the ASRS Business of Retina meeting are invaluable for learning about these contacts. If you have the benefit of working near a university, hiring a marketing graduate student can be helpful. Obviously, this person may not know the clinical details, but he or she will know how to devise a plan and connect you with the technical expertise to develop the social media and technology aspects of the campaign.

The pharma rep whose company has an interest in AMD may also be a resource, able to supply you with educational materials and perhaps even sponsor a dinner or conference to help you educate local ophthalmologists and optometrists. These companies also may have grants available that can be used to help you develop an AMD educational program.

Other organizations have printed materials that can be shared. The ASRS, for example, has retina physician-authored material that can be printed free of charge and shared with your patients. The American Academy of Ophthalmology has AMD educational videos that can be purchased and played for patients in your office waiting room; the videos can even be custom-recorded with your own voice.

Ultimately, the depth of your AMD educational effort depends on you. They can consist of a one-time push over the course of AMD Awareness Month, with just a few presentations to the local community and your referral base, or they can comprise a full-time, ongoing dedication to make your local practice an "AMD Center of Excellence," with a large campaign conducted together with a pharma/medical device company — complete with brochures, a web page, social media management, and press releases.

In either case, a good way to measure the effectiveness of your campaign is to track the number of referrals over time from each doctor or lecture. You should survey every new patient with questions such as, "Where did you hear about us?" or "Who referred you?" Other good ways to measure effectiveness are to track website hits and social media views or new followers.

WHY EDUCATE ABOUT AMD?

Better education could very well mean increased patient caseloads for the eyecare professionals in your community, including you. Importantly, you'll be helping to create better informed patients, optometrists, and ophthalmologists, and increasing awareness about the leading cause of visual impairment in people older than age 50 in developed countries. You're also building your practice's reputation.

But the best answer to the question of why is simply to help prevent vision loss. Earlier AMD diagnosis means earlier intervention, and earlier intervention leads to better outcomes. It doesn't get any clearer than that. *NRP*

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All the Right Moves

If putting down roots means relocating your practice, here are some tips for a smooth transition

BY DAVID R.P. ALMEIDA, MD, MBA, PHD

As a new retinal specialist, you've probably led a rather nomadic existence during the last few years, moving from med school to residency and fellowship, and then on to your first job. You've likely made some difficult choices along the way, perhaps leaving your extended family and your hometown in pursuit of your career goals. I've been there.

Although I was born in Lisbon, Portugal, I grew up in Canada. I attended medical school and completed an ophthalmology residency at Queen's University, Kingston, Ontario. Fully embracing the nomadic existence, I earned a PhD in pharmacology at the University of Szeged in Hungary and an MBA in Healthcare Management at George Washington University in Washington, DC. Then, my wife, who is also from Canada, and I moved to the United States, so I could complete my retina fellowship at the University of Iowa. We had a wonderful 2 years in Iowa City, and found we really liked the Midwest.

Immediately after fellowship, we moved to Minnesota, where I joined VitreoRetinal Surgery in the Minneapolis-St. Paul area. Again, it was a wonderful experience, but as our family grew — we now have 3 children, the oldest just starting kindergarten — we felt the tug of family ties and geography. As much as we enjoyed Minnesota, we thought it would be nice to live in a warmer climate closer to our extended families, most of whom live along the east coast of Canada.

This realization led us to North Carolina, where I now work as a vitreoretinal specialist at Metrolina Eye Associates, an expanding multispecialty practice based in Charlotte. The decision to move wasn't made lightly and involved months of research and planning. Here, I share some of the key factors we considered, including some that are easily overlooked.

WHY MOVE?

Right now, there's a certain element of mobility in retina practice, as we try to optimize the relationship of geography,

5 Key Logistical Issues

Moving your family to a new home and settling into a new job is a massive undertaking with many diverse components. In thinking about geography, type of practice, city, and so on, it's easy to overlook some important logistical matters. These five issues should be included on your transition checklist:

1. CONTRACT

In addition to carefully reviewing the proposed employment contract yourself, I recommend having it reviewed by a lawyer. Ask questions, negotiate, do your due diligence. You've been in practice for a few years and have gained some insights. You now know the "real retina world," so tap into that knowledge to ensure you're happy with the contract and practice circumstances.

2. UNEMPLOYMENT PERIOD

How much time are you comfortable being unemployed between jobs? You'll want to minimize uncertainty and your exposure to an extended unemployment period, but plan on a minimum of 1 month; moreover, items, such as licensing, credentialing, getting on insurance plans, and so on, can easily take 3 to 6 months, so you need to start early. If you've accepted a new position while you're still employed, you may be able to start this process before relocating.

In any case, consider taking some time off before you start your new job. I finished my fellowship training on June 30, then drove from Iowa City to Minneapolis, and started my new job on July 1. Looking back, that probably wasn't the best idea. This time around, I took a month off to spend time with my family. While you're balancing the needs of two practices to make sure everyone's happy in terms of end and start dates, be sure to find time for your personal life and your family.

3. RETIREMENT BENEFITS

You've been working and contributing to a 401(k) plan as well as other investment vehicles, and if you're lucky, your employer's been contributing, too. When you join a new practice, there will more than likely be a waiting period before you can start contributing again — 6 to 12 months is typical — so try to max out your 401(k) before you move. This is a simple technical issue that's easy to overlook.

4. HEALTH INSURANCE

During the time you're unemployed, you'll also be without health insurance. But, you may qualify for COBRA coverage, which allows you to continue your employer-sponsored health plan for a limited time.

If you choose COBRA coverage, be aware that you will be responsible for paying 100% of the premiums — including the share your employer used to pay — plus a small administrative fee. Jokingly, I told my family that none of us could get sick, because COBRA is too expensive. Seriously, though, if you have medical issues that need to be addressed or if a family member needs regular care, whether or not you take COBRA is an important decision.

5. MALPRACTICE TAIL INSURANCE

When you leave a practice, you're still legally responsible for all of the patients who were under your care. Tail insurance covers the period after you've left the practice while those patients still need care. Again, this is an issue that will impact your finances. Will your previous employer pay for this coverage? Will you need to pay for it? Are you sharing that cost? Depending on how this will be handled, that could be a large sum, and it may affect how much time you want to take off between jobs.

family, and work environment. How you prioritize these factors depends on where you are in your career and your life.

Right out of fellowship, we're most familiar with the academic world and may be eager to explore new opportunities, but regardless of whether we stay in academia or go into private practice, we start to learn what it's like to be a retina specialist in the real world.

At the same time, we may now be part of a couple and possibly have young children. Our personal and professional priorities and goals undergo rapid changes, which is why I think many of us have so much movement in the first 5 years of practice.

The overarching reason why I relocated my practice and moved 1,000 miles with my wife and children was, in a word, family, and I think that's usually the most important factor when any physician moves to a new location. The good news is that the job market for retina specialists is quite robust. With the aging of the baby boomers and the associated increase in age-related eye diseases, the demand for our services is high. The American Society of Retina Specialists and the American Academy of Ophthalmology post new retina jobs every day, and they're all over the country.

Accepting a position after fellowship may be something of an "Aha!" moment — you like the practice, you like the doctors, it seems like a great opportunity — but any subsequent move will need to be more thoroughly researched because so many more factors are in play.

First, you'll need to decide on a practice setting. Do you want to work at a university or in private practice, and if the latter, would you prefer a retina-only group or a multispecialty practice? This is a key decision to make before deciding to relocate.

Once you and your spouse or partner are sure a move will be good for your family and career, your search will likely begin with location.

WHERE TO GO?

Narrowing your search for a new location involves some serious introspection. Do you want to live in the Midwest or the East or West Coast? What about north versus south? Do you want to settle in an urban center, a medium-size city, a small town, or a rural area? Is proximity to an airport important to you?

Keep in mind that some cities are already saturated with retina specialists, while others may have a greater demand for services. And all states are not created equally when it comes to malpractice insurance, taxation, and tort reform. You'll need to research all of these factors to ascertain an optimal location.

My wife and I focused our research on the southeastern United States. We examined everything from proximity to our extended families, schools for the kids, and, of course, job opportunities for me. If your partner or significant other will also be searching for a job, that adds another layer of complexity to this already frenetic process.

Charlotte ticked off all the right boxes for us, including a wonderful opportunity with a multispecialty group where I could see a strong future. It took us a long time, and it was a tough decision to leave a place we like, but we feel we planned well for this move.

There are many other factors to consider when deciding whether — and where — to relocate. (See "5 Key Logistical Issues" on page 17 for a checklist of key considerations.)

OPTIMIZE YOUR PRACTICE SETUP

You've gained some important insights thus far in your career as you've adapted to various clinics and ORs. Now, you can have some input into how you'd like to practice: how much clinic time you want; how much OR time you want; what your role will be in research or administration.

Be proactive about these details. You may have found the right city, the right practice, the right everything — but how you envision your Monday through Friday and your weekends may be totally different from the needs of the practice.

Also, consider what your transition period will look like, day to day. Do you need to change equipment? Will you need to meet all of the referring doctors in the area? Are there referring doctors in your new practice?

This will be a somewhat tumultuous time, and you'll be eager to hit the ground running, but be sure to take the time to think things through. As you carve out your role as a key team member, your new employer will appreciate that you have a clear plan to deliver excellent patient care, because at the end of the day, that's what it's really all about.

A Family Decision

I can't stress enough the importance of good honest communication and dialogue with your spouse or partner during this process. You're changing everything in everyone's lives — your home, your kids' schools, where you shop, everything — and he or she must be an active participant in this decision.

Your partner should travel with you to all of your interviews and serve as your second set of eyes and ears. No question is too trivial. For example, will you be required to travel to distant satellite offices regularly, which means you may not be home to tuck in the kids most nights? It's not only your workplace that's changing but also your and your family's lifestyle.

Once your decision is made, be sure to accentuate the positive aspects of this move, so the entire family is looking forward to an exciting new adventure.

GO WITH CONFIDENCE

For most of us, research is part of our DNA. Once you've done your due diligence and investigated everything you know to investigate, remember that you have the training and the skill set to be successful. Finding the right fit may come down to asking yourself, "Will we be happy here?"

As for my family, I like to say we're undergoing a smooth transition. We're hoping to make Charlotte our home for a long time, and my parents, who still live in Canada, think this area could be a wonderful place for them to retire. I think we took the right steps, did the right research, and made the right move. *NRP*

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Connecting with Your Community

How to leverage the power of social media to build a successful clinical and professional career

BY PETER KARTH, MD, MBA, VITREORETINAL SURGEON AT OREGON EYE CONSULTANTS

As a new retina specialist, you have many options for jobs or career paths. You may be well on your way down a certain path, or your future may be somewhat unknown. Establishing a firm and lasting connection with your community is key, and it's something you can do right away — even if you're unsure what your future holds. This connection will help build trust, credibility, and reputation — all of which are vitally important to career success.

Social media is an excellent way to build this connection: you can choose your audience and you can choose your topic. The reach you can personally achieve is dramatic and can extend far beyond what you could otherwise attain through other methods. I believe that leveraging the power of social media can help propel you to a more successful clinical and professional career.

There are many physicians who have thousands or tens of thousands of social media connections on their professional accounts. Just imagine the impact you can have with that kind of reach on a daily basis. With a professional social media presence, you can be the thought leader you know you are and have an impact far beyond the physical world you exist in every day.

CHOOSE YOUR AUDIENCE AND TOPIC

In my opinion, the most important aspects of successful social media are to carefully choose your audience and topic and stay consistent. Choose a topic you have a passion for, something that you can commit to posting about for years, without wavering.

Think of talk radio or a podcast: if you listen to a sports show and one day you tune in and they're talking about cooking, you probably would move on. With social media "Unfriending" or "Unfollowing" takes just a click, and you probably will never get that person back. Also, posting about your passion ensures you have staying power, rather than posting for a couple weeks about a particular article you read and then quickly fading off into oblivion.

Keep in mind that your topic doesn't even have to be about the retina. Of course, choosing a clinical topic, like general eye and retina care, is the best for connecting with patients, if that's your goal. Posts for this would typically be more basic, such as "Sunlight and Your Retina" or "AMD Basics."

With this type of message, you probably won't have many fellow retina doctors or researchers as followers, because your message is likely not what they're interested in. But, by fostering this kind of connection with patients or potential patients, you can have a Dr. Oz-like online persona, as well as create a patient following that transcends your current job. In this case, remember your audience is interested in eye care, not on the score of your alma mater's homecoming game.

You can also create a professional audience of fellow retina specialists, ophthalmologists, referring providers, researchers, or innovators. For this audience, you might want to post clinical cases with compelling images, or run an online "Two-minute Journal Club." Maybe it's ethics, rants for or against the healthcare system, financing tips for physicians, or eyecare comedy. Pretty much whatever you want to talk about, you will find an audience of some kind.

SOCIAL BUTTERFLY

It goes without saying that you need the technical know-how to be active on multiple platforms, with maximum messaging impact and minimal time. None of us can afford more than a few minutes a day to manage our social media.

Over the past few years, I've been very pleased with the growth of my professional social media following. I post about "Health Tech for Eye Care," with a slant toward artificial intelligence and new health tech, which is something I really like thinking and talking about.

I've made connections and had opportunities that I never would have found without social media. For me, it has been rewarding in many ways so I recommend you give it a try. *NRP*

Coding Reassessment for Complex Retinal Detachment Repair

BY RIVA LEE ASBELL

In a recent vitreoretinal surgical coding course, the subject of what constitutes a complex retinal detachment repair evolved into a robust discussion regarding the criteria as set forth in the Current Procedural Terminology (CPT) definition. It was agreed that it was time for a discussion of the code and what types of surgery were intended to qualify a case to be coded as complex.

HISTORICAL DEVELOPMENT

In 2008, new vitrectomy codes were established in CPT and a new code for complex retinal detachment repair was initiated. Here is the new code description that went into effect Jan. 1, 2008, and has since remained unchanged:

- **67113** - *Repair of complex retinal detachment (e.g., proliferative vitreoretinopathy, stage C-1 or greater, diabetic traction retinal detachment, retinopathy of prematurity, retinal tear of greater than 90 degrees), with vitrectomy and membrane peeling, may include air, gas, or silicone oil tamponade, cryotherapy, endolaser photocoagulation, drainage of subretinal fluid, scleral buckling, and/or removal of lens*

Prior to this, a combination of CPT codes 67108 and 67038 was used:

- **67108** - *Repair of retinal detachment; with vitrectomy, any method, including, when performed, air or gas tamponade, focal endolaser photocoagulation, cryotherapy, drainage of subretinal fluid, scleral buckling, and/or removal of lens by same technique*
- **67038** - *Vitrectomy, mechanical, pars plana approach; with epiretinal membrane stripping*

Technically, CPT code 67038 was replaced with three codes in 2008:

- **67041** - *Pars plana vitrectomy; with removal of preretinal cellular membrane (e.g., macular pucker)*
- **67042** - *Pars plana vitrectomy; with removal of internal limiting membrane of retina (e.g., for repair of macular hole, diabetic macular edema), includes, if performed, intraocular tamponade (i.e., air, gas or silicone oil)*
- **67043** - *Pars plana vitrectomy; with removal of subretinal membrane (e.g., choroidal neovascularization), includes, if performed, intraocular tamponade (i.e., air, gas or silicone oil) and laser photocoagulation*

CPT code 67043 was fairly obsolete by the time the code was issued due to the development and use of various anti-VEGF drugs administered by intravitreal injection. The CPT system was slower in getting codes into the system, and codes issued in 2008 would have started their development in 2005 — about the time that Rosenfeld et al. published the first proposal for using bevacizumab (Avastin, Genentech) for treating wet AMD (preceded by the use of Macugen [pegaptanib sodium injection, Bausch + Lomb]).[1-3]

The remaining two codes were regarded as being used for removal of epiretinal membrane (67041) and removal of internal limiting membrane for repair of macular hole and diabetic macular edema (67042). Because the phrases "epiretinal membrane" and "preretinal cellular membrane/macular pucker" appeared in both codes (67038 and 67041, respectively), it was widely interpreted that use of the complex code for retinal detachment repair consisted of the combination of retinal detachment repair with epiretinal membrane peeling. This became the standard replacement for 67108 + 67038. It is important to note that both CPT codes 67041 and 67042, as well as 67043, were to be considered as replacements for 67038.

CODE DISSECTION/INTERPRETATION

Examples incorporated in the Code Description

The examples with interpretative comments as warranted include the following:

- Proliferative vitreoretinopathy, stage C-1 or greater
- Diabetic traction retinal detachment
- Retinopathy of prematurity
- Retinal tear of greater than 90 degrees

Mandatory surgical techniques in the Code Description:

- Vitrectomy
- Membrane peeling

Comment: Due to the origin of the code 67113 being 67108 + 67038, this has been widely interpreted as epiretinal membrane peeling. I would like to suggest that this encompasses all types of membrane peeling and also includes repair of macular hole. Thus, according to the CPT code descriptor, the two mandatory techniques are pars plana vitrectomy (PPV) for repair of a retinal detachment and some type of membrane peeling. Peeling of the hyaloid membrane is usually performed as part of the repair of a retinal detachment procedure and does not qualify as a mandatory technique. I have seen only rare exceptions to this.

May include the following surgical techniques (not mandatory):

- air, gas, or silicone oil tamponade
- cryotherapy
- endolaser photocoagulation
- drainage of subretinal fluid
- scleral buckling
- and/or removal of lens

Comment: Techniques used in a surgical case from this category, with rare exceptions, should not and cannot be coded separately and are bundled together in the National Correct Coding Initiative (NCCI).

CASE STUDIES

Case 1

History: A rhegmatogenous retinal detachment in the right eye had previously been repaired using silicone oil that now needed to be removed. In the global period, the patient (Type 2 diabetes mellitus) presented with proliferative diabetic retinopathy with macular edema, tractional retinal detachment, retained silicone oil, and posterior synechiae in the right eye. Surgery consisted of PPV, membrane peel- ing, posterior synechiolysis, anterior chamber washout, and endolaser.

Operative notes: "... Iris hooks were placed. Healon was used to visco-dissect the iris off the anterior capsule of the lens. A second port was placed 3 mm posterior to the limbus superonasally. The silicone oil was aspirated from the vitreous cavity. The extrusion cannula was placed into the anterior chamber and used to wash out the retained silicone oil from the anterior chamber. A third vitrectomy port was placed superotemporally. There was a very strong, dense, white membrane across the posterior pole causing a tractional retinal detachment. This membrane was segmented and delaminated as much as was possible. Air fluid exchange was performed. Endolaser was applied inferiorly ..."

Diagnoses:

1. E11.3521 - Type 2 DM with proliferative diabetic retinopathy with traction retinal detachment involving the macula, right eye
2. H43.311 - Vitreous membranes and strands, right eye
3. H21.541 - Posterior synechiae, right eye
4. T85.698A - Other mechanical complication of other specified internal prosthetic devices, implants, and grafts
5. Z98.89 - Personal history of surgery, not elsewhere classified

CASE 1

CPT CODE	MODIFIERS	ICD-10-CM CODE(S)
67113 - Repair of complex retinal detachment with vitrectomy and membrane peeling ...	-58-RT	1, 2, 3, 5
67121 - Removal of implanted material, posterior segment; intraocular	-51-58-RT	4, 5
65920 - Removal of implanted material, anterior segment of eye	-51-58-RT	4, 5

Tips:

- Modifier 58 is used to engender payment in the global period because a greater procedure (67113) is being performed after a lesser one (67108). If the coding of the prior case was 67113, then you would use modifier 78. Modifier 58 pays 100% of the allowable and a new global period begins; modifier 78 pays 70% of the allowable and the global period remains intact.
- The complex repair code mandates use of membrane peeling. Without it, CPT code 67113 cannot be used.
- More and more anterior segment surgery is being performed with posterior segment surgery. The silicone oil had migrated to the anterior chamber, so 65920 is used for its removal and CPT code 67121 is used for the removal from the posterior segment.

Case 2

History: The patient presented outside of the global period of a previous retinal detachment surgery with a combined tractional and rhegmatogenous retinal detachment and proliferative vitreoretinopathy in the left eye. Surgery consisted of PPV with repair of combined tractional and rhegmatogenous retinal detachment, membrane peeling, endolaser, anterior chamber tap, 15% C3F8 gas fill.

Operative notes: "... Closed vitrectomy was carried out under widefield visualization. The retina was detached temporally and there were fixed folds across the macula and inferiorly. There was a round break superiorly.

"Perfluron was placed over the optic disc and brought up to the posterior edge of the posterior most break. Care was taken to ensure good disc perfusion and a lack of a rise in IOP. Intraocular forceps were used to peel the proliferative tissue from the surface of the macular and the fixed folds, inferiorly. No new retina breaks were encountered. Further vitrectomy and subsequent air/fluid exchange was performed above the perfluoron bubble. The perfluoron bubble was exchanged for air. Endolaser was applied 360 degrees between the ora and the equator with care taken to surround the retinal break. There was a mild hyphema which had settled on the lens, a 25-gauge needle was placed in the AC from the temporal limbus and used to aspirate some of this blood ..."

Diagnoses:

1. H33.42 - Traction detachment of the retina, left eye
2. H33.012 - Retinal detachment (rhegmatogenous) with single break, left eye
3. H21.02 - Hyphema, left eye
4. Z98.89 - Personal history of surgery, not elsewhere classified

CASE 2

CPT CODE	MODIFIERS	ICD-10-CM CODE(S)
67113 - Repair of complex retinal detachment with vitrectomy and membrane peeling ...	-LT	1, 2, 4
65815 - Paracentesis of anterior chamber; with removal of blood, with or without irrigation and/or air injection	-51-RT	3, 4

Tip:

- Most of the procedures are bundled under the NCCI and cannot be coded additionally.

Case 3

History: The patient presented with Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema in the left eye. Examination revealed a tractional retina detachment, epiretinal membrane formation, membrane formation, and a non-clearing vitreous hemorrhage in the left eye. Surgery consisted of PPV with repair of tractional retinal detachment, epiretinal membrane peeling, removal of the internal limiting membrane, and endolaser application.

Operative notes: "... Closed vitrectomy was carried out. The anterior hyaloid was aspirated and removed from the posterior aspect of the lens to clear the vitreous hemorrhage within the vitreous. This cleared the visual axis. There was no damage to the lens.

"Further vitrectomy was performed to relieve traction between areas of vitreous and neovascularization. Bands between areas of neovascularization were cut with the vitrector.

"Once all the surface traction had been relieved, ICG dye was placed on the macula and irrigated out. The epiretinal membrane, which was creating folds in the macula, was grasped with ILM forceps and circumferentially peeled. The traction from the central macula was relieved. The internal limiting membrane was similarly removed.

"Examination of the retinal periphery using widefield visualization found no new retinal breaks. Air fluid exchange was performed. Endolaser was applied to the periphery ..."

Diagnoses:

1. E10.3522 - Type 1 DM with proliferative diabetic retinopathy with traction retinal detachment involving the macula, left eye
2. H35.372 - Puckering of macula, left eye
3. H43.12 - Vitreous hemorrhage, left eye
4. H43.332 - Vitreous membranes and strands, left eye

CASE 3

CPT CODE	MODIFIERS	ICD-10-CM CODE(S)
67113 - Repair of complex retinal detachment with vitrectomy and membrane peeling ...	-LT	1, 2, 3, 4

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EYLEA® (aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY—Please see the EYLEA package insert for full Prescribing Information.

1 INDICATIONS AND USAGE

EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of:

Neovascular (Wet) Age-Related Macular Degeneration (AMD); Macular Edema Following Retinal Vein Occlusion (RVO); Diabetic Macular Edema (DME); Diabetic Retinopathy (DR) in Patients with DME

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments. Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Dosage and Administration (2.7) and Patient Counseling Information (17)*].

5.2 Increase in Intraocular Pressure. Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately [*see Dosage and Administration (2.7)*].

5.3 Thromboembolic Events. There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.

A total of 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months.

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%
Eye pain	9%	9%
Cataract	7%	7%
Vitreous detachment	6%	6%
Vitreous floaters	6%	7%
Intraocular pressure increased	5%	7%
Ocular hyperemia	4%	8%
Corneal epithelium defect	4%	5%
Detachment of the retinal pigment epithelium	3%	3%
Injection site pain	3%	3%
Foreign body sensation in eyes	3%	4%
Lacrimation increased	3%	1%
Vision blurred	2%	2%
Intraocular inflammation	2%	3%
Retinal pigment epithelium tear	2%	1%
Injection site hemorrhage	1%	2%
Eyelid edema	1%	2%
Corneal edema	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (RVO). The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following BRVO in one clinical study (VIBRANT).

Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

Adverse Reactions	CRVO		BRVO	
	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Diabetic Macular Edema (DME). The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

Adverse Reactions	Baseline to Week 52		Baseline to Week 100	
	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.

6.2 Immunogenicity. As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [*see Animal Data*].

Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept [*see Clinical Pharmacology (12.1)*], treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.

Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.

8.2 Lactation

Risk Summary

There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA is not recommended during breastfeeding.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

8.3 Females and Males of Reproductive Potential

Contraception

Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

Infertility

There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed humans with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment [*see Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use. The safety and effectiveness of EYLEA in pediatric patients have not been established.

8.5 Geriatric Use. In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

17 PATIENT COUNSELING INFORMATION

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].

Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

Manufactured by:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

Issue Date: June 2017
Initial U.S. Approval: 2011

Based on the May 2017 EYLEA® (aflibercept) Injection full Prescribing Information.

REGENERON

POWER TO PREVAIL

As demonstrated in phase 3 clinical trials evaluating BCVA,* as measured by ETDRS letters, in patients with Wet AMD, Macular Edema following RVO, DME, and by ETDRS-DRSS† in DR in Patients with DME,[1] as well as your clinical experience

Start with EYLEA for proven efficacy outcomes[1]

AMD = Age-related Macular Degeneration; DME = Diabetic Macular Edema;
DR = Diabetic Retinopathy; RVO = Retinal Vein Occlusion.

Dosing driving efficacy outcomes across all indications.[1]
Learn more at EYLEA.us/dose

INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

EYLEA® (aflibercept) Injection is indicated for the treatment of patients with

- Neovascular (Wet) Age-related Macular Degeneration (AMD): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months).
- Macular Edema following Retinal Vein Occlusion (RVO): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly).
- Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR) in Patients with DME: The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

CONTRAINDICATIONS

- EYLEA® (aflibercept) Injection is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

Please see adjacent Brief Summary.

*Best-corrected visual acuity.
†Early Treatment Diabetic Retinopathy Study–Diabetic Retinopathy Severity Scale: an established grading scale for measuring the severity of DR.

Reference: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. May 2017.

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